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(54) Title: INTRALUMINAL DEVICE WITH A COATING CONTAINING A THERAPEUTIC AGENT

(57) Abstract: The invention relates to an intraluminal device, in particular an intraluminal prosthesis, shunt, catheter or local drug delivery device. In order to increase the bio-compatibility of this device, it is provided with at least one coating. The coating contains a therapeutic agent which is comprised in a matrix that sticks to the intraluminal device. Instead of being formed by a little bio-compatible polymer, the matrix is formed by a bio-compatible oil or fat, such as cod-liver oil or olive oil. Preferably, the bio-compatible oil or fat further comprises alfa-tocopherol.

can result in inactivation of the therapeutic agent and most polymers are not very bio-compatible and induce a foreign body inflammatory response, resulting in even more hyperplasia and restenosis.

The object of the present invention is therefore to provide a new intraluminal device which is provided with a coating which does not need an aggressive polymerisation step, which is bio-compatible and which enables to obtain a sustained local release of the therapeutic agent.

To achieve this object, the intraluminal device according to the invention is characterised in that the matrix which comprises the therapeutic agent is formed by a bio-compatible oil or fat.

It has been found rather surprisingly that an oil or fat adheres sufficiently strongly to the intraluminal device so that most of the coating remains on the intraluminal device when inserting it in the lumen. The oil or fat matrix further slows down the release of the therapeutic agent once inserted in the body lumen. Due to the selection of a bio-compatible oil or fat, the coating reduces the foreign body inflammatory response induced by the intraluminal device. A further advantage of an oil or fat coating is that it has a lubricating effect so that no further lubricants have to be used which may reduce the bio-compatibility of the intraluminal device.

By bio-compatible oil or fat is meant is the present specification that the oil or fat does not have any intolerable adverse effect on the lumen structure wherein the intraluminal device is to be applied.

The term "oil or fat" is further used to designated substances which have the physical characteristics of an oil or a fat, a fat differing only in one respect from an oil, a fat being solid at room temperature whilst an oil is liquid at room temperature. In liquid state, i.e. at a sufficiently high temperature, oils and fats have a viscous

weight and more preferably only in minor proportions, e.g. less than about 10% by weight free fatty acids. The oils or fats can further be composed of, or may comprise other fatty acid derivatives, in particular methyl or ethyl esters of fatty acids.

An example of a further "oily" or "fatty" substance which can be used as bio-compatible oil or fat is alfa-tocopherol and/or a derivative thereof such as alfa-tocopherol acetate. The alfa-tocopherol and/or a derivative thereof may either be a component of the oil or fat or the oil or fat may consist substantially entirely of this compound.

As disclosed already in EP-A-0 623 354 tocopherol (vitamin E) is a therapeutic agent. In general, in accordance with the present invention, the oil or fat forming the matrix which sticks to the intraluminal device may thus be formed partially or completely by the therapeutic agent when this therapeutic agent is an oil or a fat. Of course one or more further therapeutic agents can be incorporated in the thus formed oil or fat matrix.

The present inventors have found that alfa-tocopherol and/or derivatives thereof are preferably used in combination with an oil or fat comprising fatty acids and/or derivatives thereof, in particular one or more triglycerides. They have found more particularly that coatings containing this combination showed a very good bio-compatibility to vascular tissue. The observed effects on the decrease on the inflammation score, and especially on the decrease of the area stenosis and of the neointimal hyperplasia, indicating the occurrence of synergetic effects. The alfa-tocopherol and/or the derivatives thereof are preferably mixed with the oil or fat comprising fatty acids and/or derivatives thereof to achieve such synergetic effects but a top coat of the alfa-tocopherol and/or the derivatives thereof on a first oil or fat coating appeared to provide also good results. Such a top coat comprises preferably said alfa-tocopherol and/or said derivative thereof in an amount of at least

the oil or fat, the therapeutic agent can be dissolved therein or, when it is not soluble in the oil or fat, it can be dispersed therein, more particularly emulsified or suspended depending on the fact whether the therapeutic agent is a liquid or a solid.

The therapeutic agent may be selected from the group consisting of vinblastine, sirolimus, mitoxantrone, tacrolimus, paclitaxel, cytochalasin, latrunculin, and everolimus, a particular preference being given to everolimus. It can also be selected from the group consisting of deferoxamine, geldanamycin, nigericin, penitrem, paxilline, verruculogen, KT5720, KT5823, Anisomycin, chelerythrine chloride, genistein, parthenolide, trichostatin A, T2 toxin, Zearalenone, Interferon, epithalon-D, Ca-ionophore, 4 bromo Ca Ionophore, Aflatoxins, aphidicolin, brefeldin A, cerulenin, chromomycin A3, citrinin, cyclopiazonic acid, forsokolin, fumagillin, fumonisins B1, B2, hypericin, K252, mycophenolic acid, ochratoxin A, and oligomycin or further from the group consisting of mycophenolic acid, mycophenolate mofetil, mizoribine, methylprednisolone, dexamethasone and other corticosteroids, certican™, tritolide™, methotrexate™, benidipine™, ascomycin™, wortmannin™, LY 294002, Camptothecin™, Topotecan™, hydroxyurea, cyclophosphamide, cyclosporin, daclizumab, azathioprine, gemcitabine™, and derivatives and analogues thereof. As therapeutic agents genes, coding for certain substances (proteins), having either anti-thrombotic and/or anti-restenotic action, can be used as well.

The therapeutic agent may have different effects and may in this respect be selected amongst immunosuppressants, anti-inflammatories, anti-proliferatives, anti-migratory agents, anti-fibrotic agents, proapoptotics, calcium channel blockers, anti-neoplastics, antibodies, anti-thrombotics, anti-platelet agents, IIb/IIIa blockers, antiviral agents, anti-cancer agents, chemotherapeutics, thrombolytics, vasodilators, antibiotics, growth factor antagonists, free radical

a deleterious effect on the therapeutic agent. The melting temperature is preferably even lower than 60°C, more preferably lower than 40°C, so that a mixture can be made of the therapeutic agent, the oil or fat in its molten state and a volatile solvent such a ethanol.

In view of the fact that the release of the therapeutic agent may be too slow from the oil or fat matrix in the solid state thereof, the melting point of the oil or fat is preferably lower or equal to 37°C so that the oil or fat will be in the molten state once inserted in the body lumen.

The oil or fat may be an oil at room temperature. The above mentioned natural oils are for example liquid at room temperature, except palm oil and palm nut oil. Linseed oil, sunflower oil, corn oil, olive oil and cod-liver oil have a melting point lower or equal to about 0°C. Experiments have shown that even with such a low melting point, these oils are able to stick sufficiently strongly to the intraluminal device. However, in order to have a more stable coating, these unsaturated oils can be further stabilised by a partial hydrogenation resulting in an increase of their melting point. The melting point can be raised to a melting point higher than 10, 15, 20 or 30°C depending on the desired stability (viscosity) of the oil or fat and the release properties thereof.

When use is made of a chemically hardened oil or fat which still comprises unsaturated fatty acid chains, the hardened oil or fat is preferably free of trans isomers of unsaturated fatty acid chains. Natural oils are normally free of such trans isomers. During the usual hardening processes, trans isomers are however formed. Since such trans isomers may have negative effects, they are preferably removed, for example in accordance with the technique described in WO 98/54275.

The present invention also relates to a method for providing an intraluminal device, in particular an intraluminal prosthesis, shunt, catheter or local drug delivery device, with at least one coating containing a therapeutic agent comprised in a matrix which sticks to the intraluminal

e) Stirring of the obtained solution until achievement of a homogenous mixture/solution

f) Applying to the prosthesis body of the therapeutic agent containing oil/solvent emulsion or solution using dipcoating or spraycoating or any other coating method

g) Airdry till the solvent is evaporated.

h) Optionally repeat the previous steps multiple times, eventually using different therapeutic agents.

i) Further airdry the prosthesis in a sterile laminar flow.

Prior to step c, a therapeutic agent could already be added to the solvent or to the oil or fat. The oil or fat could for example be enriched with EPA and optionally DHA. It is also possible to add alfa-tocopherol and/or a derivative thereof to the oil or fat. Moreover, an oil or fat can be selected which comprises already groups which are therapeutically active, such as unsaturated fatty acid groups, or a therapeutic agent can be bonded to the oil or fat using any chemical bonding technique. When the oil or fat is already provided in this way with a therapeutic agent, it is not necessary any more to add a therapeutic agent although it is still possible to add further therapeutic agents. This is for example the case when the oil is formed by alfa-tocopherol or a derivative thereof or when the oil comprises alfa-tocopherol or a derivative thereof.

After drying a topcoat, consisting of a bio-compatible oil or fat, in particular a natureal edible oil or alfa-tocopherol (or an derivative thereof) or a combination thereof can be using dipcoating, spraycoating or any other coating method .

After drying, the obtained coated prosthesis can be used as such or further dried and sterilised. Light-protection of the obtained coated prosthesis is advisable to maintain the bio-compatible characteristics when stored.

Thus the present invention provides a prosthesis which may be delivered and expanded in a selected body lumen or conduit without losing a therapeutically significant amount of a drug or gene applied thereto. It also provides a drug or gene containing prosthesis which allows for a sustained release of the drug or gene to luminal or conduit tissue.

The underlying structure of the prosthesis used according to the invention can be virtually any prosthesis design, for example of the self-expanding type or of the balloon expandable type, and of metal or polymeric material. Thus metal prosthesis designs such as those disclosed in US-A-4.733.665 (Palmaz) and US-A-5.603.721 (Lau) could be used in the present invention. Also prosthesis with special surface treatments or special designs to optimise local drug delivery are especially suitable for this invention ( for example: DE199 16 086 A1, EP O 950 386 A2, EP 1 132 058 A1, WO 01/66036 A2, WO 98/23228, US 5.902.266, US 5.843.172, ...). The surface of the prosthesis could in particular be provided with perforating holes or pits which can be filled with the coating material to increase the load of therapeutic agent and/or to slow down the release. After having applied the coating, the surface of the prosthesis next to the holes or pits can be wiped off or cleaned to remove the coating material. The present invention therefore does not only embrace continuous coatings covering the entire prosthesis but also discontinuous local coatings or combinations of local coatings and continuous top coatings applied thereover. The coating further does not need to be applied on the surface of the prosthesis. When using for example porous prostheses, the coating may be located within the pores of the prosthesis. The prosthesis could be made of virtually any bio-compatible material having physical properties suitable for the design. For example, tantalum, nitinol and stainless steel have been proven suitable for many such designs and could be used in the present

and dipped in a bicarbonate solution and air-dried, then dipcoated in the oil coating solution. The coated stents were air-dried or sterilized with ethylene oxide before implantation in porcine coronary arteries. The surface characteristics of the coated stents were examined by light and scanning electron microscopy (SEM).

Stent implantation

Domestic cross bred pigs of both sexes, weighing 20-25kg were used. They were fed with a standard natural grain diet without lipid or cholesterol supplementation throughout the study. All animals were treated and cared for in accordance with the Belgium National Institute of Health Guidelines for care and use of laboratory animals.

Acute Study

In this study control bare stents and oil coated stents (cod-liver oil (CLO), alfa-tocopherol oil solution (VIT E), CLO+VIT E, in each group 5 stents) were randomly implanted in the coronary arteries of pigs. Pigs were sacrificed after 5 days to evaluate acute inflammatory response and thrombus formation.

Chronic Study

In this study control bare stents (n=16) and oil coated stents (CLO n=13, VIT E n=16, CLO+VIT E n=3) were implanted randomly in the coronary arteries of pigs. Pigs were sacrificed after 4 weeks to evaluate peri-strut inflammation and neointimal hyperplasia.

Surgical procedures and stent implantation in the coronary arteries were performed according to the method described by De Scheerder et al in "Local angiopeptin delivery using coated stents reduces neointimal proliferation in overstretched porcine coronary arteries." J. Inves. Cardiol. 8:215-222; 1996, and in "Experimental study of thrombogenicity and foreign body reaction induced by heparin-coated coronary stents." Circulation 95:1549-1553; 1997.

2 = more pronounced, covering the stent filament;

3 = big thrombus resulting in an area stenosis of <50%;

4 = big thrombus resulting in an area stenosis>50%.

The mean score was calculated as the sum of scores for each filament/ number of filament present.

Morphometric analysis of the coronary segments harvested was performed on 3 slices (proximal, middle and distal stent part) by using a computerized morphometry program (Leitz CBA 8000). The areas of respectively the arterial lumen, the area inside the internal elastic lamina (IEL), and the area inside the external elastic lamina (EEL) were measured. Furthermore, the area stenosis (1-lumen area/IEL area) and the area of neointimal hyperplasia (IEL area - lumen area) were calculated.

Statistics

For comparison among different groups, the non-paired t-test is used. Data are presented as mean value ±SD. A p value $\leq$ 0.05 was considered as statistically significant.

Results

SEM images of the coated stents

The thickness of coating covering the stent filaments was 10 µm. The stent surface was smooth .

Histopathologic findings (Table 1)

At 5 days follow-up, the bare and all CLO coated stents induced an identical histopathological response. The stent filaments showed a good alignment to the vascular wall. Internal elastic membrane was beneath the stent filaments and the media was compressed. Arterial injury induced by stent implantation was not significant different among the groups. A thin fibrin layer covering the stent filaments was observed. A few inflammatory cells trapped within a thrombotic meshwork covering the stent struts were observed. No significant different inflammatory

Conclusion

All three coated and bare stents elicited a similar tissue response at 5 days follow-up. No additional inflammatory response and increased thrombus formation were observed with coated stents at that time point. At 4 weeks follow-up, all coated stents showed a mild inflammatory response. The inflammatory scores of coated stents were lower than the bare stents, especially using the VIT E coating. CLO and CLO+VIT E coated stents showed a decreased neointimal hyperplasia compared to the bare stents. The decreased lumen area of VIT E coated stents may be caused by smaller selected stented arteries as the neointimal hyperplasia of VIT E coated stents was comparable to bare stents.

In conclusion, all CLO, VIT E and CLO+VIT E coatings showed an excellent bio-compatibility to vascular tissue and could therefore serve as a vehicle for local drug delivery. The best results were obtained with the CLO+VIT E combination.

Olive oil coatings

In addition to the tests with cod-liver oil and vit. E oil, similar tests have been done with olive oil. The results of these tests are shown in Table 2. In this table it can be seen that, compared to the results for the bare stents given in Table 1, a coating consisting of only olive oil has beneficial effects on the lumen area, the neointimal hyperplasia and the area stenosis.

Tacrolimus loaded into the biological oil

To evaluate this new coating method use was made as endoluminal prosthesis of a commercial available balloonexpandable coronary stent (V-Flex Plus, 16mm/3.0mm, William Cook Europe). As drug we used Tacrolimus, a calcineurin inhibitor, which blocks IL-2 mediated T-cell proliferation and possesses anti-inflammatory and anti-proliferative activity.

Tacrolimus (1mg) was dissolved in an emulsion of 50% highly purified eicosapentaenoic (EPA) enriched oil and 50% pure ethanol. After intense stirring during 5 min a homogeneous solution was obtained. Stents were cleaned and degreased and dried. They were dipped in a Sodium bicarbonate solution during 30 seconds, air-dried and than dipped in the Tacrolimus/eicosapentaenoic(EPA) enriched oil/ethanol emulsion.

The stents were air-dried in a warm laminar flow to let evaporate the ethanol and a thin, homogeneous coating layer was obtained. Stents were repeatedly (3X) dipped and dried . Thereafter the stents were immerced in an alfa-tocopherol/ethanol solution and again airdried.

Total Tacrolimus amount obtained on one stent was 800µg.

In vitro drug release showed a progressive release of the drug over 4weeks.

In vivo experiments using a porcine coronary model revealed perfect biocompatibility of the coating system. No inflammatory response was seen at 5, 10days, and 4 and 8 weeks after stent inplantation. Using the coating without the drug an unexpected 20% reduction of in-stent neointimal hyperplasia compared with non-coated bare stents was observed at 4 and 8 weeks. Adding tacrolimus, the neointimal hyperplasia could be further decreased.

more preferably more than 10% and most preferably more than 15% by weight of unsaturated fatty acids.

8. A device according to claim 7, characterised in that said unsaturated fatty acids comprise eicosapantaenoic acid and optionally decosahexaenoic acid.

9. A device according to any one of the claims 6 to 8, characterised in that said oil or fat further comprises alfa-tocopherol, and/or a derivative thereof such as alfa-tocopherol acetate, the oil or fat comprising the alfa-tocopherol, and/or the derivative thereof, preferably in an amount of between 20 and 80% by weight, more preferably in an amount of between 30 and 70% by weight.

10. A device according to any one of the claims 6 to 9, characterised in that said oil or fat comprises less than 50% by weight, preferably less than 10% by weight of free fatty acids.

11. A device according to any one of the claims 1 to 10, characterised in that said oil or fat comprises an either or not chemically modified, in particular partially hydrogenated, animal or vegetable oil, in particular fish oil, olive oil, linseed oil, sunflower oil, corn oil and/or palm or palmnut oil, the oil comprising preferably fish oil, in particular cod-liver oil and more particularly purified cod-liver oil containing more than 90% by weight of triglycerides.

12. A device according to any one of the claims 1 to 11, characterised in that said coating comprises at least 50% by weight, preferably at least 70% by weight, more preferably at least 80% by weight and most preferably at least 90% by weight of said oil or fat.

13. A device according to any one of the claims 1 to 12, characterised in that said coating comprises at least 70% by weight, preferably at least 85% by weight and most preferably at least 95% by weight of said oil or fat and said therapeutic agent.

sirolimus, mitoxantrone, tacrolimus, paclitaxel, cytochalasin, latrunculin, and everolimus.

22. A device according to any one of the claims 1 to 21, characterised in that said therapeutic agent comprises at least one therapeutic agent selected from the group consisting of deferoxamine, geldanamycin, nigericin, penitrem, paxilline, verruculogen, KT5720, KT5823, Anisomycin, chelerythrine chloride, genistein, parthenolide, trichostatin A, T2 toxin, Zearalenone, Interferon, epithalon-D, Ca-ionophore, 4 bromo Ca Ionophore, Aflatoxins, aphidicolin, brefeldin A, cerulenin, chromomycin A3, citrinin, cyclopiazonic acid, forsokolin, fumagillin, fumonisins B1, B2, hypericin, K252, mycophenolic acid, ochratoxin A, and oligomycin.

23. A device according to any one of the claims 1 to 22, characterised in that said therapeutic agent comprises at least one therapeutic agent selected from the group consisting of immunosuppressants, anti-inflammatories, anti-proliferatives, anti-migratory agents, anti-fibrotic agents, proapoptotics, calcium channel blockers, anti-neoplastics, antibodies, anti-thrombotics, anti-platelet agents, IIb/IIIa blockers, antiviral agents, anti-cancer agents, chemotherapeutics, thrombolytics, vasodilators, antibiotics, growth factor antagonists, free radical scavengers, radiopaque agents, anti-angiogenesis agents, angiogenesis drugs, cyclooxygenase inhibitors, phosphodiesterase inhibitors, cytokine inhibitors, nitrogen oxide donors, and cytokine activators.

24. A device according to any one of the claims 1 to 23, characterised in that said therapeutic agent comprises at least one therapeutic agent selected from the group consisting of mycophenolic acid, mycophenolate mofetil, mizoribine, methylprednisolone, dexamethasone and other corticosteroids, certican™, tritolide™, methotrexate™, benidipine™, ascomycin™, wortmannin™, LY 294002,

# INTERNATIONAL SEARCH REPORT

Interl ial Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/54 A61L29/16 A61L31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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